DOI:10.1111/j.1477-2574.2012.00538.x

HPB

ORIGINAL ARTICLE

Pancreatoenteral anastomosis or direct closure of the pancreatic remnant after a distal pancreatectomy: a single-centre experience

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Abstract

Background: A major complication of a distal pancreatectomy (DP) is the formation of a post-operative pancreatic fistula (POPF). In spite of the utilization of numerous surgical techniques no consensus on an appropriate technique for closure of the pancreatic remnant after DP has been established yet. The aim of this study was to analyse the impact of pancreatoenteral anastomosis (PE) vs. direct closure (DC) of the pancreatic remnant on POPF.

Methods: A total of 198 consecutive patients who underwent a distal pancreatectomy between 2002 and 2010 at our institution were retrospectively analysed for post-operative morbidity and mortality.

Results: One hundred and fifty-one patients (76.3%) received DC whereas PE was performed in 47 patients (23.7%). The incidence of POPF was higher in the DC group (22% vs. 11%), whereas the rate of post-operative haemorrhage was higher in the PE group (11% vs. 7%). However, these differences were not significant. Additionally, there were no significant differences in overall post-operative morbidity and mortality between the groups.

Conclusions: The performance of PE instead of DC may be considered as a safe alternative in individual patients, but it does not significantly lead to a general improvement in post-operative outcome after DP. An interdisciplinary collaboration in the prevention and treatment of POPF therefore remains essential.

Received 29 February 2012; accepted 23 June 2012

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Introduction

A distal pancreatectomy (DP) was first performed by Billroth in 1884 and is defined as the resection of pancreatic parenchyma to the left side of the superior mesenteric vein.[1] Current indications for DP include malignant and benign lesions of the pancreas corpus and tail as well as chronic pancreatitis and trauma.[2,3] Distal carcinomas typically show a late onset of clinical symptoms and therefore are often large and unresectable at presentation.[4,5] Hence DP is performed less frequently than resections of the pancreas head region. Recent advances in operative technique and peri-operative management have reduced the mortality rate, which is reported to be less than 3% after pancreatic resections.[6,7] However, operation-associated morbidity after DP still remains high and ranges from 10% to 40% as well in high volume centres.[6,8] Post-operative pancreatic fistula formation (POPF) as the most common and clinically relevant complication is associated with local and general problems such as the formation of intra-abdominal abscesses, delayed gastric emptying, post-pancreatectomy haemorrhage and sepsis.[7] Patient age, duct obstruction, trauma and the texture of the pancreas tissue have been identified as potential risk factors for POPF.[9] Additionally, surgical techniques are considered as a major risk factor, and therefore, numerous modifications have been described in an attempt to optimize the procedure on the pancreatic remnant. These techniques include hand-sewn sutures or stapled closure (or a combination of both), ultrasonic dissection, pancreatoenteral anastomosis, application of meshes and sealing by use of fibrin glue.[10–15] The two most established techniques, hand-sewn sutures and stapled closure, were recently compared in a randomized, controlled, multicentre study.[16] No benefit of performing stapled closure instead of hand-sewn sutures could be

This study was presented at the EHPBA 2011 meeting in Cape Town, South Africa, during E-AHPBA Poster Session (P0032P) and recommended for publication by the moderators Dr R. Charnley and Dr S. Shrikhande.

demonstrated, and a total POPF incidence of 30% was found.[16] Other studies have reported particularly divergent results regarding the closure technique, with an incidence of POPF between 32% and 60%.[17,18] Another technique, the performance of a PE as pancreatojejunostomy (PJ) or pancreatogastrostomy (PG), has become more common recently, especially in patients with an underlying 'hard' tissue remnant as in chronic pancreatitis. However, this technique has only been investigated in small sample studies, and no benefit could be demonstrated in comparison to direct closure (DC).[12–14] The aim of this present study was to compare the significance of a PE vs. DC of the pancreatic stump at a high-volume tertiary care centre, with the main focus on post-operative morbidity and mortality.

Patients and methods

Study design

A retrospective analysis of 198 consecutive patients who underwent a distal pancreatectomy between 1st February 2002 and 1st June 2010, at the Department of General, Visceral and Transplantation Surgery at Charité University Hospitals, Berlin, Campus Virchow was performed. In this study, surgeons were trained and experienced in both performing DC (hand-sewn sutures or stapled closure) or PE (PJ or PJ), and the decision on the type of proceeding with the pancreatic remnant was individually determined. Medical records from a prospective database of pancreatic resections were reviewed, and data were documented in a Windows Excel table format. The patients were then divided into two groups depending on the type of procedure performed for the pancreatic remnant (DC vs. PE). The type of DC (hand sutures vs. stapling) and the location of the PE (pancreatojejunostomy vs. pancreatogastrostomy) were documented, and patient data were reviewed for selected pre-operative and operative data as well as for postoperative morbidity and mortality.

Surgical technique

A distal pancreatectomy was always performed as open surgery. At laparotomy, hepatic or peritoneal metastases were initially excluded by complete exploration of the stomach. A decision on whether to perform an additional splenectomy was performed by the surgeon taking the underlying disease into account. Access to the omental bursa was established by splitting of the gastrocolic ligament from the left to the right side and preparing the vasa gastroepiploica. After retraction of the stomach and inspection of the pancreas surface were performed, local resectability of the lesion and the extent of the resection (i.e. the need for additional organ resection) were determined based on local findings such as vascular and/or other organ infiltration. If the lesion was resectable, the lower margin of the pancreas was prepared by incision of the retroperitoneum to mobilize, and, if possible, tunnel under, the pancreas. In cases of underlying malignant disease, a standard lymphadenectomy was performed. After preparation of the portal vein, a wooden flute was inserted into the space anterior to the veins and posterior to the corpus of the pancreas. If a splenectomy was performed as a next step, the splenic artery was sewn over close to the outflow of the celiac trunk using 4-0 Prolene sutures and was peripherally ligated. The pancreas was then cut through the left of the superior mesenteric vein using electrocautery. After separation of the left side of the pancreas from the retroperitoneum under careful preservation of the left adrenal gland and ligation of the lienal vein at the junction of the portal vein, the pancreas and spleen were then removed from the situs. Subsequent closure of the main pancreatic duct of the pancreatic remnant was achieved by a stitch ligation using 4-0 Prolene sutures. A DC of the pancreas remnant was either performed using hand sutures with 4-0 Prolene sutures placed in the form of 'U' shapes or using a linear stapling device (Ethicon TL 60 1.0–2.5 mm, Johnson & Johnson Medical GmbH, Norderstedt, Germany) armed with a 60-mm magazine. In case of a pancreatoenteral anastomosis, either a pancreatojejunostomy or a pancreatogastrostomy was performed using mattress sutures placed in a 'U' shape combined with two corner sutures. Every patient received at least one intra-abdominal drain (Degania Silicone Europe GmbH, Regensburg, Germany) to measure post-operative lipase/amylase levels and drain output. Pancreatic tissue texture was assessed intra-operatively by the operating surgeon and was considered as either 'soft' or 'hard'.

Standard post-operative care

All patients were monitored for at least one day at our surgical intensive care unit. Amylase and/or lipase levels were monitored daily in the serum and in the intra-operatively placed abdominal drains on the first and fourth post-operative day. Routine perioperative antibiotics [Cefuroxime 1 g intravenously (i.v.) and Metronidazole 500 mg i.v.] were given. Subcutaneous somatostatin therapy (100 μg) was routinely administered three times daily in the post-operative course. In the absence of signs of a pancreatic fistula, oral food intake was begun depending on the clinical presentation and tolerance.

The diagnosis of a POPF was based on the definition of the International Study Group on Pancreatic Fistula (ISGPF).[19] According to the ISGPF definitions Grades A, B, and C fistulae were considered as POPF. However, the levels of amylase in the intra-operatively placed drains were not available for all subjects in our database. The lipase levels in the drains were always measured. We therefore slightly modified the ISGPF definitions and used amylase or lipase levels in the drains to define the existence of a POPF.

Post-pancreatectomy haemorrhage (PPH) was also defined based on the ISGPF definitions.[20] In addition to the clinical presentation, the diagnosis of a dehiscence of the pancreatoenteric anastomosis was based on radiological and/or operative confirmation.

Statistical analysis

For the statistical analysis, PASW Statistics 19 (SPSS Software, IBM Company, Chicago, IL, USA) was used. For continuous vari-

ables, the median was reported with the range. Analysis of specific-risk factors was performed using *t*-tests or the Mann-Whitney *U*-test. Categorical variables were described using frequencies and percentages. For categorical variables, chi-square tests were used. A *P*-value <0.05 was defined as significant.

Results

Patient baseline data

Between 1st February 2002 and 1st June 2010, a total of 198 consecutive distal pancreatectomies were performed at the Department of General, Visceral and Transplantation Surgery at Charité University Hospitals, Berlin, Campus Virchow. Of these, in 151 patients (76%), a DC of the pancreas remnant was performed, whereas in 47 patients (24%), a PE was performed. There were 108 males (55%) and 90 females (45%), with a median age of 61 years (range, 17–88). The indication for distal pancreatectomy was pancreatic adenocarcinoma in 114 patients (58%), chronic pancreatitis in 16 patients (8%), pancreas pseudocyst in 12 patients (6%), metastasis to the pancreas in 7 patients (4%), gastric carcinoma in 16 patients (8%), neuroendocrine tumour in 16 patients (8%) and other indications (ganglioneuroma, gastrointestinal stromal tumour, kidney carcinoma, duodenal carcinoma and liposarcoma) in 17 patients (9%). Patients with chronic pancreatitis underwent operations for intractable pain. As an additional surgical procedure, a splenectomy was performed in 173 patients (84%), liver resection in 15 patients (8%), partial or total gastrectomy in 45 patients (23%) and oesophageal resection in 4 patients (2%) (Table 1).

Table 1 Characteristics of the patients

	Direct closure of pancreas remnant (DC)	Pancreatoenteral anastomosis (PE)
Number of patients	151	47
Median age (range)	62 (17–88)	57 (26–87)
Gender (male)	84 (56%)	24 (51%)
Indication		
Pancreatic carcinoma	95 (63%)	19 (40%)
Chronic pancreatitis	8 (5%)	8 (17%)
Pancreas pseudocyst	7 (5%)	5 (11%)
Metastasis	2 (1%)	5 (11%)
Gastric carcinoma	16 (11%)	0
Neuroendocrine tumour	11 (7%)	5 (11%)
Others	12 (8%)	5 (11%)
Median operation time	230 min	227 min
Additional organ resection		
Splenectomy	129 (85%)	45 (96%)
Partial/total gastrectomy	39 (26%)	6 (13%)
Liver resection	13 (9%)	3 (6%)
Oesophagal resection	4 (3%)	0
Pancreas tissue texture		
Soft	103 (68%)	21 (45%)
Hard	32 (21%)	20 (43%)
Not assessed	16 (11%)	6 (13%)

Direct closure of the pancreas remnant vs. pancreatoenteral anastomosis

The median operation time was 230 min when performing a DC of the pancreas remnant using either hand sutures or a stapling device vs. 227 min when performing a PE either as PG or PJ. In the DC group pancreas tissue texture was found to be 'soft' in 103 patients (68%), 'hard' in 32 patients (21%) and not assessed in 16 patients (11%). In the PE group, pancreas tissue texture was documented as 'soft' in 20 patients (43%), 'hard' in 21 patients (45%) and not assessed in 6 patients (13%). The incidence of major post-operative morbidity after DC of the pancreas remnant was 26% (39/151) in comparison to 19% (9/47) after performing a pancreatoenteral anastomosis. A POPF occurred in 22% (33/151: Grade A 7%, Grade B 7% and Grade C 7%) of the patients after DC vs. 11% (5/47: Grade A 4%, Grade B 4%, Grade C 2%) of the patients after pancreatoenteral anastomosis. The incidence of POPF in patients with an underlying 'soft' pancreas tissue remnant was 23% (24/103) in the DC group vs. 14% (3/21) in the PE group. In patients with an underlying 'hard' pancreas tissue the incidence of POPF was 16% (5/32) in the DC group and 10% in the PE (2/20) group.

The incidence of PPH was 7% (11/151) in the DC group vs. 11% (5/47) in the PE group. The median length of hospital stay was 20 days in the DC group vs. 19 days in the PE group. However, these differences were not significant. The overall mortality was 4% after DC (6/151) and 2% after PE (1/47). Four patients died as a result of PPH: two patients died because of septic multi-organ-failure and one patient died because of acute cardiac failure. There were no significant differences regarding operative factors or post-operative morbidity and mortality between the two groups (Table 2).

Direct closure of the pancreas remnant: hand sutures vs. stapler device

Hand sutures were used as the closing technique of the pancreas remnant in 136 patients (90%), whereas a stapler device was used for closure in 15 patients (10%). The median operation time was 235 min when performing hand sutures in comparison to 193 min when using a stapler device for pancreatic remnant closure. Major morbidity occurred in 25% (34/136) and POPF in 21% (28/136) of the patients after hand sutures in contrast to an incidence of major morbidity of 40% (6/15) and POPF of 33% (5/15) after stapler device closure. However, these differences were not significant. Additionally, there were no significant differences between the groups in the rates of re-operation (14% vs. 20%), the median length of hospital stay (19 days vs. 28 days) and overall mortality (4% vs. 0%). The incidence of PPHs was significantly

Table 2 Post-operative patient factors and morbidity

	Closure of pancreas remnant (*n* = 151)	Pancreatoenteral anastomosis (*n* = 47)	*P*-value
Median operation time (SD)	230 (±86) min	227 (±71) min	NS
Major morbidity	39 (26%)	9 (19%)	NS
POPF	33 (22%)	5 (11%)	NS
POPF Grade A	11 (7%)	2 (4%)	NS
POPF Grade B	11 (7%)	2 (4%)	NS
POPF Grade C	11 (7%)	1 (2%)	NS
PPH	11 (7%)	5 (11%)	NS
Re-operation	21 (14%)	7 (15%)	NS
Median hospital stay	20 days	20 days	NS
Mortality	6 (4%)	1 (2%)	NS

NS, non-significant (significant if <0.05).

Table 3 Closure of the pancreas remnant: hand sutures vs. stapler

	Hand suture (*n* = 136)	Stapler (*n* = 15)	*P*-value
Median operation time (SD)	235 (± 88) min	193 (±53) min	NS
Major morbidity	34 (25%)	6 (40%)	NS
POPF	28 (21%)	5 (33%)	NS
POPF Grade A	10 (7%)	1 (7%)	NS
POPF Grade B	9 (7%)	2 (13%)	NS
POPF Grade C	9 (7%)	2 (13%)	NS
PPH	8 (6%)	3 (20%)	0.05
Re-operation	19 (14%)	3 (20%)	NS
Median hospital stay	19 days	28 days	NS
Mortality	6 (4%)	0	NS

NS, non-significant (significant if <0.05); POPF, post-operative pancreatic fistula formation.

higher ($P = 0.05$) when performing a stapler closure (3/15 or 20%) in comparison to hand suture closure of the pancreatic remnant (8/136 or 6%) (Table 3).

Pancreatoenteral anastomosis: pancreatojejunostomy vs. pancreatogastrostomy

A pancreatojejunostomy was performed for PE in 38 patients (81%). Nine patients (19%) received a pancreatogastrostomy. There were no significant differences in the median operation time (231 min vs. 213 min), the incidence of post-operative morbidity (16% vs. 33%), the formation of POPF (11% vs. 11%) or PPH (8% vs. 22%). There were also no significant differences in the rate of relaparotomy (16% vs. 11%) or the median hospital stay (20 days vs. 17 days). However, the overall mortality was significantly increased ($P = 0.04$) when a PG was performed (1/9 or 11%) than when a PJ was performed (0/38) (Table 4).

Risk factors for POPF

According to the ISGPF definitions, POPF Grade A occurred in 13 patients (7%), Grade B in 13 patients (7%) and Grade C in 12 patients (6%). Thus, the total incidence of POPF was 19% (38/198). Individual risk factors identified for POPF were patient's age greater than 65 years, operation time greater than 300 min and an additional organ resection. The performance of a DC or PE did not show a significant impact on POPF.

Discussion

The clinical outcome in pancreatic surgery has improved considerably in the last decades with a consistent reduction of post-operative morbidity and mortality.[21] However, with a reported incidence of 10% to 40%, POPF remains the most common and clinically relevant complication after DP.[6,8] POPF is associated with complications such as pancreatic fluid collection, intra-abdominal abscesses, wound infection and sepsis, and therefore also has a significant effect on health care costs and resources.[22] Pratt *et al.* emphasized the economic burden of POPF and demonstrated that costs increased in tandem with the severity Grade of POPF.[23] Poor nutritional status (defined as low albumin and/or recent weight loss), advanced patient age, male gender, higher body mass index, duct obstruction and 'soft' pancreatic tissue have been identified as risk factors for POPF.[7,9,24] In addition, various technical factors including the method of stump closure, concomitant organ resection (i.e. splenectomy), transfusion of erythrocyte concentrates and a longer operation time were shown to correlate with an increased risk for POPF.[7,8] Surgically, the procedure performed on the pancreatic stump remains the 'Achilles heel' of DP, and therefore, numerous modifications of the operative technique for reducing the occurrence of POPF have been undertaken, although a gold standard has not been established yet. A systematic review by Knaebel *et al.* revealed that the hand-sewn closure and stapler closure were the two most common techniques for DP.[18] Kleef *et al.* observed a significantly increased risk of POPF with stapled closure, whereas other investigators have reported increased POPF rates with sutured closure of the pancreatic remnant.[7,11,25] To further complicate matters, other studies have shown no differences between the two methods in the post-operative outcome.[9,10,26]

In this study, the majority of DCs were performed using hand sutures in 136 patients (90%) in comparison to stapler closure in 15 patients (10%). Hand-sewn sutures carry the risk of tearing, especially of the duct sutures, whereas in the case of stapling, if pancreatic sutures are torn out or the tissue tears, small parts of the pancreatic cutting surface are not sealed, and POPF can occur. Additionally, Eguschi *et al.* speculated that 'hard' pancreatic tissue is more likely to be crushed when compressed by a stapler.[27]

Table 4 Pancreatoenteral anastomosis: pancreatogastrostomy vs. pancreatojejunostomy

	Pancreatojejunostomy (*n* = 38)	Pancreatogastrostomy (*n* = 9)	*P*-value
Median operation time (SD)	231 (± 72)min	213 (± 68)min	NS
Major morbidity	6 (16%)	3 (33%)	NS
POPF	4 (11%)	1 (11%)	NS
POPF Grade A	1 (3%)	1 (11%)	NS
POPF Grade B	2 (5%)	0	NS
POPF Grade C	1 (3%)	0	NS
PPH	3 (8%)	2 (22%)	NS
Re-operation	6 (16%)	1 (11%)	NS
Median hospital stay	20 days	17 days	NS
Mortality	0	1 (11%)	0.04

NS, non-significant (significant if <0.05); POPF, post-operative pancreatic fistula formation.

Thus, at this institution hand sutures are considered the standard procedure for DC. Stapler closure was performed in the context of the DISPACT study, a recent randomized, controlled, multicentre study..[16] The results of our study demonstrated no differences between hand and staple sutures for closure of the pancreatic remnant with respect to operation time, the incidence of POPF or post-operative morbidity and thereby reflect the results of the DISPACT study.

In patients with an underlying 'hard' pancreas tissue, the performance of a PE may be a safe option. Additionally, if there is a duct obstruction in the pancreatic head or periampullary region, then the risk of POPF may be reduced when performing a PE. The performance of a PE is limited by the extent of the pancreatic resection because a marginally sized remnant from the right side of the pancreas can only be mobilized enough to perform a PE. In our study, a PE was performed in 20 patients (43%) with an underlying 'hard' pancreas tissue remnant and in 21 patients (45%) with tumours located in the distal pancreatic tail. The type of PE, PJ vs. PG, needs to be evaluated individually. PG allows good endoscopic accessibility of the anastomosis region. However, during DP PG is often limited by the difficult mobilization of the pancreatic head and body remnant and PJ is therefore often more safe and simple to perform. In this study, nine patients (19%) received PG. PJ was performed in 38 patients (81%). No significant differences in postoperative outcome could be demonstrated.

As a conclusion of this study a benefit of performing a PE, whether performed as PJ or PG, instead of a DC of the pancreatic remnant, whether with hand-sewn sutures or a stapler device, could not be demonstrated with regard to operative or post-operative outcome. Other small cohort studies have also failed to confirm a reduced incidence of POPF for PE during a distal pancreatectomy.[12,14] Owing to the small sample sizes, the non-randomized study designs and inconsistent definitions for POPF, the impact of PE remains hard to interpret. Other authors have also suggested that POPF after a PE could result in potentially more hazardous complications (such as activation of pancreatic enzymes and bacterial contamination) than POPF after a DC.[7] As an interdisciplinary approach to reduce the incidence of POPF after DP, Abe *et al*. suggested pre-operative endoscopic pancreatic stenting to prevent pancreatic leakage.[28] They reported no POPF but found a 20% incidence of mild to acute pancreatitis after stent placement. As a result of this risk of pre-operative pancreatitis and, therefore, a potential delay in the beginning of surgical treatment options, especially in oncological patients, we do not include pre-operative stenting as a standard procedure at this institution. Oida *et al*. described a potential alternative to pre-operative stenting by inserting transduodenal pancreatic juice drainage during DP in 10 patients and reported no POPF.[29] However, their study was limited by the small sample size. Post-operative pancreatic stenting showed good results in the treatment of POPF but has not been established yet as a routinely prophylactic procedure to reduce the POPF rate after DP.[30]

The results of this study also emphasize that additional organ resection, such as a splenectomy or oesophageal, stomach or liver resection, is associated with an increased rate of POPF as well as post-operative morbidity, in general, after DP. Extended surgery results in more blood loss, longer hospital stay and increased mortality. Additionally, extension of the surgery can lead to compromised healing of the pancreatic remnant as a result of a reduced blood supply of the cut surface; this explains the increased risk for POPF.[31] Nevertheless, in the presence of an oncological indication for DP, we are often left with no other choice but additional organ resection (i.e. splenectomy, gastrectomy or partial liver resection) in an attempt to optimize the oncological outcome. However, the indication for a splenectomy should be carefully evaluated in underlying benign diseases.

As in other fields of surgery, laparoscopic techniques have also been reported for DP, and laparoscopic DP (LDP) is now considered a safe and effective treatment for benign and borderline malignant tumours of the pancreas.[32] In a recent study, Mehta *et al*. reported a significant reduction in blood loss and hospital stay after performing a LDP in comparison to an open DP and

showed no differences in overall morbidity and POPF.[33] However, not all surgeons are qualified for LDP. Furthermore, left-sided pancreas cancers often present in a locally advanced stage by the time of diagnosis, and therefore LDP does not always allow a sufficient regional dissection to perform an oncological effectual resection.

The statistical power of this study is surely limited by the small sample size of patients. Furthermore, the retrospective study design may have lead to a selection bias in how patients were chosen for PE. However, the results of our study demonstrate that both, DC and PE, may safely be performed. POPF remains a major problem after DP although with a major impact on the postoperative course and postoperative outcome in general. The ideal type of procedure with the pancreatic stump, DC vs. PE, can only be individually evaluated and may therefore contribute to some reduction in POPF rate. In spite of further attempts to optimize the surgical technique, emphasis also needs to be placed on a more interdisciplinary approach in pre-operative prevention and post-operative management of POPF.

Addendum

F.K. collected the data and wrote the paper, M.G. collected the data, W.F. collected the data, S.G. collected the data, P.N. designed and performed the research and M.B. designed and performed the research. All authors contributed to the design and interpretation of the study and to further drafts.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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